Published in final edited form as:

Psychiatry Res. 2010 February 28; 181(2): 97–100. doi:10.1016/j.psychres.2009.08.005.

Orbital frontal cortex in treatment naïve pediatric obsessive-compulsive disorder

Frank MacMaster, Anvi Vora, Phillip Easter, Carrie Rix, and David Rosenberg *

Department of Psychiatry & Behavioral Neurosciences, Wayne State University, Children's Hospital of Michigan, Detroit, MI, USA 48201

Abstract

The orbital frontal cortex (OFC) has been implicated in obsessive-compulsive disorder (OCD). Twenty-eight treatment-naïve pediatric OCD patients and twenty-one controls were examined using magnetic resonance imaging. OCD patients had larger right but not left OFC white matter volume than controls. This is fresh evidence implicating white matter in OCD.

Keywords

magnetic resonance imaging; obsessive-compulsive disorder; orbital prefrontal cortex

1. INTRODUCTION

The cortical-striatal-thalamic circuit is consistently implicated in obsessive-compulsive disorder (OCD) (MacMaster et al., 2008). A critical brain region in this circuit is the orbital frontal cortex (OFC). The OFC is the most ventral portion of the prefrontal cortex and has rich connections to the amygdala and dorsomedial thalamus (Zald and Kim, 1996a), areas implicated in pediatric OCD (Gilbert et al., 2000; Smith et al., 2003; Szeszko et al., 2004b; Mirza et al., 2006). Functionally, the OFC plays a role in sensory processing, linking affective value to reinforcing stimuli, and in decision-making (Zald and Kim, 1996b; Kringelbach, 2005). These functions may be disrupted in OCD. Indeed, animal models have supported the role of the OFC in OCD as lesions to the OFC induce compulsive behaviors (i.e. lever pressing) (Joel et al., 2005a; Joel and Klavir, 2006). This effect appears region specific as lesions to the dorsal medial prefrontal cortex and basolateral nucleus of the amygdala did not cause an increase in compulsive behavior (Joel et al., 2005b). Treatment in lesioned animals with SSRI (paroxetine) diminished compulsive behaviors (Joel et al., 2005a).

In vivo neuropsychological studies have indicated a role of the OFC in OCD (Abbruzzese et al., 1995; Rosenberg et al., 1997a). Furthermore, in vivo imaging studies implicate the OFC in OCD. Szeszko et al (1999) found smaller OFC volumes in adult OCD patients as compared to controls. Early PET studies of OCD found greater OFC metabolism in patients (Nordahl et al., 1989; Baxter et al., 1990). Indeed, a recent meta-analysis of PET and fMRI studies of OCD

© 2009 Elsevier Ireland Ltd. All rights reserved.

*Department of Psychiatry & Behavioral Neurosciences, Wayne State University, 9B-UHC, 4201 St. Antoine, Detroit, MI 48201; fax: 313-577-5900, telephone: 313-577-9000, and drosen@med.wayne.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

noted that dysfunction in the OFC, along with the striatum, was the most consistent finding across reports (Whiteside et al., 2004). Using a symptom provocation paradigm, Rauch et al (1994) found a significant increase in relative regional cerebral blood flow during the OCD symptomatic state vs. the resting state in bilateral OFC. The single 1H-MRS of the OFC in OCD found increased Glx/Cr concentrations in OFC white matter in adult patients as compared to controls (Whiteside et al., 2006). Glx/Cr ratios were also correlated with OCD symptoms in patients. Finally, our preliminary studies linking genetic and neuroimaging data have noted a significant association between increased left but not right orbital frontal volume and the rs1805476 variant of GRIN2B and the SLC1A1 rs3056-AA genotype in psychotropic-naïve pediatric patients with OCD (Arnold et al., 2009). The above reports clearly implicate the OFC in the pathophysiology of OCD and in mediating OCD symptoms. Here, we present data on regional OFC volumes in pediatric OCD patients vs. healthy controls. Based on previous findings in adult OCD, we hypothesized that smaller OFC volumes would be found (Szeszko et al., 1999).

2. METHODS

2.1. Subjects

Twenty-eight psychotropic-naïve patients with OCD, aged 8 -18 years, and 21 healthy control participants (9 to 18 years) underwent volumetric magnetic resonance imaging (MRI) to evaluate orbital frontal volume (see table 1). Some of these subjects have been presented previously (11/21 controls and 10/28 OCD patients)(Gilbert et al., 2000), though not for OFC volumes. Participants were recruited through the child psychiatry outpatient clinic at Wayne State University School of Medicine in Detroit, MI. Healthy controls were recruited via advertisement, community/pediatric and school referral. The patients' diagnoses were made by a board-certified child and adolescent psychiatrist (DRR) using DSM-IV criteria and the Kiddie Schedule for Affective Disorders and Schizophrenia of School – Age Children – Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). Exclusion criteria described in previous reports (Szeszko et al., 2004a) include: lifetime history of unipolar or bipolar disorder, psychosis, eating disorders, substance abuse or dependence, Sydenham's chorea, tic-related conditions, conduct disorder, significantly debilitating medical or neurological conditions, pervasive developmental disorder, mental retardation, or learning disorder. Healthy comparison subjects had no history of psychiatric illness (nor their first-degree relatives). Legal guardians provided written informed consent, and all subjects provided written assent prior to all studies being initiated. OCD symptom severity was assessed with the Children's Yale Brown Obsessive-Compulsive Scale (Hanna, 1995). The Hamilton Depression Rating Scale (Hamilton, 1967) was used to measure depression, and the Hamilton Anxiety Rating Scale (Hamilton, 1959) was used to measure anxiety.

2.2. Magnetic Resonance Imaging (MRI)

All MRI scans were conducted at 1.5 Tesla (Horizon 5.7, General Electric, Milwaukee) at the Children's Hospital of Michigan. Parameters were: 3D spoiled gradient echo pulse sequence, 124 contiguous coronal slices, 0.94mm×0.94mm in plane, thickness = 1.5mm, TR = 25 ms, TE = 5 ms, flip angle = 40°, FOV= 180mm × 240mm, matrix = 256×192, and scan time = 7.73 minutes. Axial proton density/T2-weighted images were used by a pediatric neuroradiologist to exclude clinical abnormalities. All OFC volumes were measured using the manual tracing technique by a trained, reliable rater (PE, ICC > 0.9) blind to subject diagnosis (Szeszko et al., 1999). Briefly, the OFC was measured in the coronal plane with measurement beginning at the most anterior slice where the horizontal remus of the anterior lateral fissure (AHR) first became visible. The anterior edge of the insular cortex, which disrupts the posterior portion of the AHR, was manually landmarked before OFC measurement and care was taken to ensure that it was excluded from measurements. Left and right OFC measures were conducted separately using

the olfactory sulcus as the medial boundary and the AHR and the anterior portion of the insular cortex (as it disrupted the posterior portion of the AHR) as the lateral boundaries. The edge of the cerebral cortex was the inferior boundary, while the superior border was delineated by connection of the deepest parts on the superior frontal sulcus and the lateral fissure. Measurement of the OFC ended when the olfactory sulcus became disrupted by CSF. OFC measures were segmented with IDL imaging software (<http://www.itivis.com/ProductServices/IDL.aspx>) to obtain separate measures of gray and white matter volume.

2.3. Statistical Analysis

An analysis of covariance (ANCOVA) was used to compare groups (age, ICV and gender as covariates). For this exploratory study, alpha was set at 0.05. Pearson correlations were used to examine the relationship between regional OFC volumes and clinical variables.

3. RESULTS

Right OFC white matter was significantly larger in OCD patients as compared to controls ($p = 0.024$). No other differences in OFC were noted (table 1). In OCD patients, increased compulsive symptom severity, as measured by CY-BOCS, was positively correlated with OFC gray matter (right: $r = 0.44$, $p = 0.02$; left: $r = 0.40$, $p = 0.03$). No laterality difference was noted in OFC gray matter in either group. No significant correlation between clinical variables and right OFC white matter were noted (compulsions: $r = 0.32$, $p = 0.099$). No correlations between OFC subdivisions and age, depressive or overall anxiety symptoms were noted. In controls, left OFC white matter was greater than right OFC white matter ($t = 2.21$, $df = 20$, $p = 0.039$) but no right – left difference was seen in OCD patients. No laterality difference was noted in OFC gray matter in either group.

4. DISCUSSION

We found larger right OFC white matter volume in OCD as compared to healthy controls. This is consistent with our previous studies that found a larger corpus callosum, particularly the genu, in pediatric OCD patients (Rosenberg et al., 1997b ; MacMaster et al., 1999). Functions of the OFC, like sensory/affective processing and decision-making may be disrupted in OCD. In animal models, OFC lesions induce compulsive behaviors (i.e. lever pressing) (Joel et al., 2005a; Joel and Klavir, 2006). Treatment of lesioned animals with SSRI (paroxetine) diminished compulsive behaviors (Joel et al., 2005a). Both neuropsychological (Abbruzzese et al., 1995; Rosenberg et al., 1997a) and neuroimaging studies (Whiteside et al., 2004) of OCD have indicated a role of the OFC in OCD. More recently, our group has published a preliminary study that found a significant association between increased left OFC volume and variants of the glutamate receptor gene (GRIN2B) and the glutamate transporter gene (SLC1A1) in psychotropic-naïve pediatric OCD patients (Arnold et al., 2009). Certain polymorphisms for oligodendrocyte lineage transcription factor 2 (OLIG2) are associated with OCD (Stewart et al., 2007). OLIG2 is an essential regulator in the development of cells that produce myelin. Furthermore, increased fractional anisotropy in a right medial frontal region has been noted in OCD (Menzies et al., 2008). These studies provide corroborative evidence for our finding of increased right OFC white matter in pediatric OCD and indicate a possible genetic underpinning. In healthy children, diffusion-imaging studies have shown a differential right frontal developmental trajectory (Schmithorst et al., 2008). This may explain why OFC white matter was lateralized in the controls. As for the finding of larger ICV in OCD patients as compared to controls, larger total brain white matter has been noted in OCD previously (Atmaca et al., 2007). It may also be a developmental effect (i.e. early myelination) that becomes less apparent during adulthood.

This work is somewhat counter to the previous study of the OFC in adults with OCD, which found smaller overall (gray and white) OFC volumes in patients as compared to controls (Szeszko et al., 1999). However, those subjects were medicated (Szeszko et al., 1999) and that may have affected volume measures, similar to the thalamus in pediatric OCD (Gilbert et al., 2000). It may also be that myelination of the OFC white matter occurs earlier or more extensively in OCD patients and that difference is lost over development. It is unlikely that comorbid depressive or general anxiety symptoms influenced the findings. Limitations include the small sample size, and a lack of developmental data. Future studies include diffusion tensor imaging to look at the related tracts and longitudinal studies of the OFC development.

REFERENCES

- Abbruzzese M, Bellodi L, Ferri S, Scarone S. Frontal lobe dysfunction in schizophrenia and obsessive-compulsive disorder: a neuropsychological study. *Brain and Cognition* 1995;27:202–212. [PubMed: 7772333]
- Arnold PD, MacMaster FP, Hanna GL, Richter MA, Sicard T, Burroughs E, Mirza Y, Easter PC, Rose M, Kennedy JL, Rosenberg DR. Glutamate system genes associated with ventral prefrontal and thalamic volume in pediatric obsessive-compulsive disorder. *Brain Imaging and Behavior* 2009;3:64–76.
- Atmaca M, Yildirim H, Ozdemir H, Tezcan E, Poyraz AK. Volumetric MRI study of key brain regions implicated in obsessive-compulsive disorder. *Progress In Neuro-Psychopharmacology & Biological Psychiatry* 2007;31:46–52. [PubMed: 16859819]
- Baxter LR Jr, Schwartz JM, Guze BH, Bergman K, Szuba MP. PET imaging in obsessive compulsive disorder with and without depression. *Journal of Clinical Psychiatry* 1990;51(Suppl):61–69. discussion 70. [PubMed: 2182617]
- Gilbert AR, Moore GJ, Keshavan MS, Paulson LA, Narula V, MacMaster FP, Stewart CM, Rosenberg DR. Decrease in thalamic volumes of pediatric patients with obsessive-compulsive disorder who are taking paroxetine. *Archives of General Psychiatry* 2000;57:449–456. [PubMed: 10807485]
- Hamilton M. The assessment of anxiety states by rating. *British Journal of Medical Psychology* 1959;32:50–55. [PubMed: 13638508]
- Hamilton M. Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology* 1967;6:278–296. [PubMed: 6080235]
- Hanna GL. Demographic and clinical features of obsessive-compulsive disorder in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry* 1995;34:19–27. [PubMed: 7860451]
- Joel D, Doljansky J, Roz N, Rehavi M. Role of the orbital cortex and of the serotonergic system in a rat model of obsessive compulsive disorder. *Neuroscience* 2005a;130:25–36. [PubMed: 15561422]
- Joel D, Doljansky J, Schiller D. ‘Compulsive’ lever pressing in rats is enhanced following lesions to the orbital cortex, but not to the basolateral nucleus of the amygdala or to the dorsal medial prefrontal cortex. *European Journal of Neuroscience* 2005b;21:2252–2262. [PubMed: 15869522]
- Joel D, Klavir O. The effects of temporary inactivation of the orbital cortex in the signal attenuation rat model of obsessive compulsive disorder. *Behavioral Neuroscience* 2006;120:976–983. [PubMed: 16893303]
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry* 1997;36:980–988. [PubMed: 9204677]
- Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. *Nature Reviews. Neuroscience* 2005;6:691–702.
- MacMaster FP, Keshavan MS, Dick EL, Rosenberg DR. Corpus callosal signal intensity in treatment-naïve pediatric obsessive compulsive disorders. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 1999;23:601–612. [PubMed: 10390719]

- MacMaster FP, O'Neill J, Rosenberg DR. Brain imaging in pediatric obsessive-compulsive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2008;47:1262–1272. [PubMed: 18827717]
- Menzies L, Williams GB, Chamberlain SR, Ooi C, Fineberg N, Suckling J, Sahakian BJ, Robbins TW, Bullmore ET. White matter abnormalities in patients with obsessive-compulsive disorder and their first-degree relatives. *American Journal of Psychiatry* 2008;165:1308–1315. [PubMed: 18519525]
- Mirza Y, O'Neill J, Smith EA, Russell A, Smith JM, Banerjee SP, Bhandari R, Boyd C, Rose M, Ivey J, Renshaw PF, Rosenberg DR. Increased medial thalamic creatine-phosphocreatine found by proton magnetic resonance spectroscopy in children with obsessive-compulsive disorder versus major depression and healthy controls. *Journal of Child Neurology* 2006;21:106–111. [PubMed: 16566872]
- Nordahl TE, Benkelfat C, Semple WE, Gross M, King AC, Cohen RM. Cerebral glucose metabolic rates in obsessive compulsive disorder. *Neuropsychopharmacology* 1989;2:23–28. [PubMed: 2803479]
- Rauch SL, Jenike MA, Alpert NM, Baer L, Breiter HC, Savage CR, Fischman AJ. Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. *Archives of General Psychiatry* 1994;51:62–70. [PubMed: 8279930]
- Rosenberg DR, Averbach DH, O'Hearn KM, Seymour AB, Birmaher B, Sweeney JA. Oculomotor response inhibition abnormalities in pediatric obsessive-compulsive disorder. *Archives of General Psychiatry* 1997a;54:831–838. [PubMed: 9294374]
- Rosenberg DR, Keshavan MS, Dick EL, Bagwell WW, MacMaster FP, Birmaher B. Corpus callosal morphology in treatment-naïve pediatric obsessive compulsive disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 1997b;21:1269–1283. [PubMed: 9460091]
- Schmithorst VJ, Holland SK, Dardzinski BJ. Developmental differences in white matter architecture between boys and girls. *Human Brain Mapping* 2008;29:696–710. [PubMed: 17598163]
- Smith EA, Russell A, Lorch E, Banerjee SP, Rose M, Ivey J, Bhandari R, Moore GJ, Rosenberg DR. Increased medial thalamic choline found in pediatric patients with obsessive-compulsive disorder versus major depression or healthy control subjects: a magnetic resonance spectroscopy study. *Biological Psychiatry* 2003;54:1399–1405. [PubMed: 14675804]
- Stewart SE, Platko J, Fagerness J, Birns J, Jenike E, Smoller JW, Perlis R, Leboyer M, Delorme R, Chabane N, Rauch SL, Jenike MA, Pauls DL. A genetic family-based association study of OLIG2 in obsessive-compulsive disorder. *Archives of General Psychiatry* 2007;64:209–214. [PubMed: 17283288]
- Szeszko PR, MacMillan S, McMeniman M, Chen S, Baribault K, Lim KO, Ivey J, Rose M, Banerjee SP, Bhandari R, Moore GJ, Rosenberg DR. Brain structural abnormalities in psychotropic drug-naïve pediatric patients with obsessive-compulsive disorder. *American Journal of Psychiatry* 2004a;161:1049–1056. [PubMed: 15169693]
- Szeszko PR, MacMillan S, McMeniman M, Lorch E, Madden R, Ivey J, Banerjee SP, Moore GJ, Rosenberg DR. Amygdala volume reductions in pediatric patients with obsessive-compulsive disorder treated with paroxetine: preliminary findings. *Neuropsychopharmacology* 2004b;29:826–832. [PubMed: 14970831]
- Szeszko PR, Robinson D, Alvir JM, Bilder RM, Lencz T, Ashtari M, Wu H, Bogerts B. Orbital frontal and amygdala volume reductions in obsessive-compulsive disorder. *Archives of General Psychiatry* 1999;56:913–919. [PubMed: 10530633]
- Whiteside SP, Port JD, Abramowitz JS. A meta-analysis of functional neuroimaging in obsessive-compulsive disorder. *Psychiatry Research* 2004;132:69–79. [PubMed: 15546704]
- Whiteside SP, Port JD, Deacon BJ, Abramowitz JS. A magnetic resonance spectroscopy investigation of obsessive-compulsive disorder and anxiety. *Psychiatry Research* 2006;146:137–147. [PubMed: 16507346]
- Zald DH, Kim SW. Anatomy and function of the orbital frontal cortex, I: anatomy, neurocircuitry; and obsessive-compulsive disorder. *Journal of Neuropsychiatry and Clinical Neurosciences* 1996a;8:125–138. [PubMed: 9081547]
- Zald DH, Kim SW. Anatomy and function of the orbital frontal cortex, II: Function and relevance to obsessive-compulsive disorder. *Journal of Neuropsychiatry and Clinical Neurosciences* 1996b;8:249–261. [PubMed: 8854295]

Figure 1.
Representative multi-slice composite series of coronal images demonstrating the boundaries of the orbital frontal cortex (OFC).

Table 1

Summary of Demographics and Findings

Item	OCD Patients	Healthy Controls	Statistic
Age (Years)	12.78 ± 2.92	13.56 ± 2.88	t = 0.93, p = 0.36
Sex	14 Males 14 Females	9 Males 12 Females	X ² = 0.18, p = 0.67
CY-BOCS	24.61 ± 5.74	-	-
Duration of Illness (Months)	47.14 ± 38.10	-	-
Hamilton Depression Scale	8.07 ± 5.35	-	-
Hamilton Anxiety Scale	8.39 ± 4.64	-	-
OFC Right Gray (cc)	5.67 ± 1.49	5.45 ± 1.57	F = 0.52, df = 4,47, p = 0.85
OFC Right White (cc)	3.86 ± 0.73	3.17 ± 0.83	F = 5.50, df = 4,47, p = 0.024*
OFC Left Gray (cc)	5.92 ± 1.30	5.75 ± 1.93	F = 0.92, df = 4,47, p = 0.34
OFC Left White (cc)	3.83 ± 0.83	3.75 ± 1.27	F = 0.90, df = 4,47, p = 0.35
Intracranial Volume (cc)	1235.79 ± 108.27	1142.75 ± 114.93	t = 2.90, df = 4,47, p = 0.006*